

#### IV

## ACTIVE IMMUNISATION BY INTRACUTANEOUS INJECTION OF LIVE GONOCOCCUS CULTURES AS A THERAPEUTIC MEASURE IN CHRONIC GONORRHŒA OF THE CERVIX AND ADNEXA IN WOMEN

### EXPERIENCE WITH OVER 10,000 INJECTIONS

By ALFRED A. LOESER (London), late Consulting Gynæcologist of the Municipal Hufeland Hospital, Berlin ; late Director of the Gynæcological Department of the Israelitic Hospital, Berlin ; L.R.C.P. and S. Edin. ; M.D. Berlin.

Short Historical Introduction.

Deep-seated Infection in Chronic Gonorrhœa, Histology of Cervical Gonorrhœa.

Active Immunisation with Living Gonococci.

Report of 10,102 Injections with Live Gonococcus Cultures.

Complications and Possible Dangers of the Method.

Geographical Influences on Gonorrhœa.

Comparison of Active Immunisation with other Therapeutic Methods.

Summary.

Bibliography.

Other methods than the ones usually employed have been followed by me during the last fifteen years to combat the incurable consequences of chronic gonorrhœa in women. In all parts of the world chronic gonococcal infection of the female genitalia plays an important part in national health, impairs fertility and may remain a permanent danger for fresh infection. Only the experiences and researches of generations of doctors have rendered it cumulatively possible to elaborate a new therapy and it is my grateful duty before discussing my own researches to make a brief retrospective review.

More than 100 years ago, Ricord was the first to show clearly the clinical difference between gonorrhœa and other venereal diseases. Later, Neisser proved that the gonococcus was the causal factor of gonorrhœa. Bumm,

## ACTIVE IMMUNISATION

who, with Neisser, I have the honour to regard as my mentor, was the first to succeed in making cultures of the gonococcus, thus rendering it possible to treat gonorrhœa with a suspension of killed gonococci and to inject increasing doses of such killed gonococcus cultures into human tissue (Bruck) in accordance with the methods of Wright, the father of vaccine therapy. I went a step further and injected live gonococcus cultures, after having proved on myself, as a healthy individual, that live gonococci, injected into or beneath the skin, remain at the site of injection and are more or less quickly killed by the surrounding skin tissue. This was the first step towards an active immunisation. During the last fifteen years my investigations have been verified so often and found to be of use that I want here to give a summary of this extensive work and to complete the account with a list of the publications that have appeared in medical journals in various parts of the world.

Acute and chronic gonorrhœal infections are in women two fundamentally different pathological processes, depending upon the tissue layers in which the disease develops. In acute gonorrhœa there is always a superficial infection of the mucosa of the genital passages ; and in chronic cervical and adnexal gonorrhœa always a deep-seated infection of the tissues below the mucosa. It is therefore not difficult to cure acute gonorrhœa by applying antiseptics to the mucosa ; on the other hand, it is improbable that deep-seated processes as found in chronic gonorrhœa can be affected by medicaments which do not penetrate deeply into the tissues. Even if one applies to the cervical canal such disinfectants as Mesodin (Flavadin) which claim to have a certain penetrative power, and even if local remedies to kill all bacteria existing on the surface of the cervical mucosa are employed, it is doubtful if any such treatment can reach the deeper parts of the glands where colonies of gonococci are localised behind barriers of inflammatory tissue. Sulphanilamide may have the best effect in this respect.

## HISTOLOGY OF CERVICAL GONORRHŒA

The histological study of uteri chronically infected with gonococci has advanced during recent years, particularly through the researches of Schroeder,<sup>46</sup> and Felke and

Oettingen,<sup>12</sup> and finally Felke in 1936. Extensive inflammatory changes take place in the gland tissue, sometimes reaching as far as the muscular regions. Periglandular infiltrates of round cells and plasma cells may be found at the gland terminals, and in the fundus of the glands small abscesses containing gonococci may form. The glandular epithelium is metaplastically replaced by stratified squamous epithelium. Schroeder recorded such changes in 20 uteri removed by operation, and Felke and Oettingen demonstrated similar deep-seated mutations in 6 cases.

I myself am in a position to report in detail a case which was submitted to histological and bacteriological examination. In removing a very elongated cervix during an operation necessitated by prolapsus uteri, I came across some yellowish spotted parts in cutting through the cervix from which pus exuded. These patches were situated beneath the cervical mucosa. Both microscopical and bacteriological examination revealed gonococcus. The patient now admitted what she had before this denied, that about two years previously she had been infected with gonorrhœa, which had been treated with the usual remedies. Histologically, cervical glands cut in serial sections were found covered with squamous epithelium. This squamous epithelium was arranged in manifold strata so that the examining pathologist (Professor Pick, Berlin) at first suspected incipient carcinoma. The musculature showed infiltration of round cells and plasma cells and at the gland terminals small deep-lying abscesses were situated. Sexual intercourse during two years had not passed the infection to her partner. In the cervical canal itself no gonococci were found. Does not this case suggest that locally applied medicaments cause the gonococci to disappear from the surface without curing the infection, which persists behind a barrier of metaplastic epithelium and inflammatory infiltrates, the gonococci remaining alive and able to break the barrier on the occasion of any tissue stimulation, menstruation or pregnancy, and become, once again, a source of infection? It even strikes me that by applying local remedies too frequently and too freely a fillip is given to the development of chronic gonorrhœa. That gradually these deep-seated foci are destroyed by natural tissue resistance is possible, and well known. To combat these

## ACTIVE IMMUNISATION

deep-seated foci effectively it is necessary to have recourse to vaccines. The gonococcus vaccines found in commerce lose their potency unless very recently prepared. Old killed vaccines have only a very limited activity and many injections stretching over a number of weeks are necessary. In previous contributions I have shown that freshly made vaccines are more effective, but unfortunately they evoke very high temperatures and unpleasant sequelæ. I was the first to recommend the injection of killed vaccines direct into the cervical tissue in the neighbourhood of the deep-seated gonococcal processes. The results thus obtained are far superior to those when the injection is made at a distance away from the infection. Bucura<sup>4 5 6 7</sup> also used this technique in his later investigations and it has erroneously been ascribed to him. From this, Basset and Poincloux developed their vaccination *à la porte d'entrée*, which is nothing more than to inject round the infected tissues; a modification of my technique described in 1922 (Loeser<sup>27</sup>).

Nevertheless, such treatment carried out locally at the site of infection, was not satisfactory. A true immunisation is obtained only by implanting living and active organisms, the site of injection being the intracutaneous tissue.

### TECHNIQUE OF INJECTING LIVE GONOCOCCI

The gonococci which I use must originate from a fresh and, if possible, untreated male or female gonococcal infection; this is the first condition. These gonococci are grown on ascites agar but must not go beyond three to four subcultures, that is, after remaining for forty-eight hours on such a plate, the gonococci must be injected as pure culture within ten days of their removal from the human body. The longer the gonococci are cultured away from human tissue, the more avirulent they become and the less useful for our purpose. Gonococci which have been subcultured for a long time in the laboratory are so mutated that they can no longer be regarded as able to stimulate sufficient antibodies. Freshly grown gonococcus strains of this kind may be produced with ease in every bacteriological laboratory. It is advisable to grow various strains and, finally, to

## BRITISH JOURNAL OF VENEREAL DISEASES

pool these, in order, if possible, to give the physician a polyvalent living vaccine.

Up to this point the work belonged to the realm of the bacteriologist, but now the technical application of the living gonococcus vaccine so produced is within the sphere of the physician.

To the tube containing the mixed, fresh, forty-eight hour old gonococcus culture on ascites agar, the dilution of which, according to repeated counts, varies between 8,000 to 12,000 million, 3 c.c. of sterile physiological salt solution are added from a sterile syringe. The tube is shaken, by which action most of the culture becomes suspended in the salt solution and with the help of a good platinum needle previously sterilised by thorough heating, the remaining culture is scraped from the nutrient medium. One notices how the culture separates from the medium in the form of slimy threads. These slimy cultures are better than the flaky cultures occasionally met with. After the culture has been suspended in the salt solution, 1.5 c.c. of this suspension is transferred to a sterile syringe by inclining the tube and then it is slowly injected intracutaneously into the left upper arm. It is not advisable first to pour the culture from the tube into another vessel, and then syphon off with the syringe, since this takes too long and the culture might die or become impaired, moreover, it militates against a strictly aseptic technique.

One may simplify the whole procedure by ordering from the bacteriologist a fresh, forty-eight hour ascites culture and injecting 1.5 c.c. of this bouillon after vigorous shaking.

The injection is carried out in the same way as one proceeds in infiltrating tissue for anæsthetisation. The needle is slowly and gently inserted obliquely beneath the skin, remaining dimly visible to the eye, and the injection of the suspended culture is made slowly into the skin with the formation of two to three wheals.

This procedure causes no pain. Each patient received 4,000–5,000 million organisms and two patients may be treated from each tube.

To prevent any small rise in temperature after the injection (the patient may be treated as an out-patient and need not remain in the hospital), salicylates are

## ACTIVE IMMUNISATION

given. The local reaction with this treatment is greater than with killed gonococcus vaccines, but the general reaction is much weaker, comparing similar doses.

### WHAT ARE THE EFFECTS UPON THE LATENT GONORRHEAL FOCI AFTER THE INJECTION ?

In many cases the injection causes the gonococci to disappear suddenly from the discharge, which becomes less and poorer in leucocytes. Sometimes the gonococci remained permanently absent.

Whereas in some cases the gonococci disappear immediately after the injection, in others a very marked increase of gonococci is noticed and the discharge is more profuse ; but these conditions abate after some days and a permanent absence of gonococci follows.

In the great majority of cases the gonococcus content of the discharge gradually diminishes, to cease entirely after eight to twenty-one days.

The injection, which to-day I carry out only intracutaneously should be repeated after seven days, even when no more gonococci can be found in the discharge. One often notices that the site of the first injection again reddens, even swells, for a short time after the second injection. A third injection is given again after seven days, this treatment for active immunisation taking twenty-one days to complete.

It has been justly objected by some investigators that it is difficult to obtain live fresh gonococcus cultures as required. A live vaccine is available on the market under the name of Gonovitan (Saechsische Serumwerke, Dresden, Germany), which represents to a certain extent a substitute for the live fresh culture. An ampoule of Gonovitan contains a living gonococcus culture which is injected in the same way as the fresh culture ; it keeps on the average three months. This preparation is to be regarded as an attenuated culture which I myself have not used, since naturally the results cannot be so good as with fresh culture. The reactions produced by it are not less than these called forth by a fresh culture. As many later investigators have used Gonovitan, it is included in the table given below.

# BRITISH JOURNAL OF VENEREAL DISEASES

## STATISTICS OF INJECTIONS OF LIVE GONOCOCCUS CULTURES, REPORTED IN INTERNATIONAL LITERATURE

The statistics divide into two sections. Under section I are again included the 1,900 injections which were reported by seventeen different authors during the years 1922-31 and which I discussed together with my own experiences (Loester<sup>36</sup>). In sections 2-23 the injections of other authors during the period between 1931 and April 1st, 1937, are classed together.

	Name of Author.	No. of Injections.
1.	Collective statistics 1922-31 (seventeen authors), Loeser <sup>26</sup>	1,900
2.	Abraham <sup>1</sup>	30
3.	Bertoloty <sup>3</sup>	222
4.	Edel <sup>8</sup>	249
5.	Feilchenfeld, I, <sup>9</sup>	27
6.	Feilchenfeld, II, <sup>10</sup>	40
7.	Felke and Oettingen <sup>12</sup>	200
8.	Friboes <sup>14</sup>	250
9.	Hussel <sup>19</sup>	250
10.	Jarecki <sup>20</sup>	324
11.	Jacobsohn (personal report)	100
12.	Kahn <sup>21</sup>	237
13.	Linde <sup>25</sup>	200
14.	Linde and Timochina <sup>26</sup>	204
15.	Langer <sup>22</sup>	180
16.	Loeser, 1931-37	189
17.	Popescu <sup>43</sup>	190
18.	Schroeder <sup>45, 46</sup> , Schwab <sup>47</sup> , Thomson <sup>52</sup>	175
19.	Schultz <sup>44</sup>	300
20.	Smirnow <sup>48</sup>	733
21.	Sommer <sup>49</sup>	72
22.	Waldeyer <sup>57</sup>	ca. 30
23.	Wolff, 1931-37 (personal report) and <sup>58-64</sup>	4,000
	Total	10,102

10,102 injections are thus involved which have been administered during the last fifteen years to more than 3,000 men and women suffering from gonorrhœa. These injections include patients treated by Wolff, Sommer,

## ACTIVE IMMUNISATION

Abraham and Feilchenfeld as well as 20 of Schroeder's patients, with attenuated live vaccine (Gonovitan).

The methods adopted by the above-mentioned authors were not always the same. Some injected subcutaneously, some intracutaneously, Schroeder <sup>47</sup> intramuscularly. The indications, also, varied greatly. Some of the cases were of a chronic nature and had been treated unsuccessfully by other methods. Others again represented acute and subacute types of female and male gonorrhœa. Polyvalent gonococcus cultures (Linde <sup>26</sup>) were also used. The results were particularly satisfactory in all cases of gonorrhœal arthritis. All authors are in agreement that in early gonorrhœal arthritis live vaccine treatment is the method of choice—there was not a single failure, Hussel <sup>19</sup> even obtained successes in more chronic articular cases. Bier stresses in particular the rapid analgesic effect of the injection. Most authors observed that the vaccine had no effect upon superficial mucosal gonorrhœa of the urethra and of the rectum, which findings were in accordance with my own observations. Most of the authors administered two or three injections of various, generally increasing, strengths and in most cases urethra and cervix were treated also locally.

*The average percentage of complete cures amounted to 80-85 per cent., and with some investigators reached as much as 95 per cent. Waldeyer was the sole exception, who reported only 50 per cent. This author deals with only 20 cases.*

### MY OWN CASES

In a previous article (Loeser <sup>35</sup>) I reported on 168 cases of chronic gonorrhœa in women, of which 113 were cured with only one injection of live virulent gonococcus culture. The technique then used differs from the one I now adopt. Moreover, at that time, I preferred to give one injection only. During the period 1931-37 I was unable owing to outside circumstances to treat and subsequently examine more than 63 women, to whom 189 injections were administered. The following changes have been made in my previous method of procedure. On principle, three injections at intervals of seven days are now always given; 1.5 c.c. of salt solution in which the culture is suspended constitutes the first dose, this corresponding to about 4,000-5,000 million organisms,



## BRITISH JOURNAL OF VENEREAL DISEASES

the second and third doses are raised to 3 c.c. corresponding to a culture of 8,000 to 12,000 million organisms. Whereas I previously restricted myself to chronic cases, I now also include cases of cervical gonorrhœa with acute ascending infection. Hussel<sup>19</sup> describes a case in which an acute gonorrhœal exudate into the pouch of Douglas or acute gonorrhœal parametritis as well as acute salpingitis following upon cervical gonorrhœa was successfully treated with intracutaneous live vaccine. I have since observed in 8 cases of ascending gonorrhœa with high temperatures instant arrest of pathological processes accompanied by an immediate feeling of well-being, and I would now, contrary to my previous convictions, always recommend injections in this condition. In 3 cases an auto-vaccine was prepared. It should further be mentioned that amongst the 63 patients, 2 were pregnant. Particularly in pregnancy, where drastic methods of all kinds, even local, are prohibited, the injections are effective and free from danger. I would like to stress the good results in affections connected with the joints and tendon sheaths. Contrary to Bertoloty<sup>3</sup> I have not observed an effect in really acute cases of urethral gonorrhœa. The striking changes occurring in adnexal gonorrhœa treated in this way are the rapid cessation of pain and of the feeling of continual discomfort in the abdomen; further, the palpably evident return to normal size of the adnexa which had been very large and adherent. Of the 63 cases, 49 were cured by three injections, *i.e.*, 76 per cent. My percentage of cures therefore increased with my new technique, although I have not yet obtained such high percentages as other investigators. This brings me to the question of the permanency of the cure and of the specificity of the treatment.

### PERMANENCY OF THE CURE AND SPECIFICITY OF THE VACCINE TREATMENT

I consider a permanent cure one in which subsequent examinations during a period of six months, carried out after or during menstruation, prove negative for gonococci. I proceed as follows. As soon as the last injection has been given, a control test is made during the next menstrual period, or, if preferred, immediately

## ACTIVE IMMUNISATION

following. Gonococci are more frequently found during menstruation than just after. If one wishes to examine after the period, it is desirable to insert a thin sound covered with cotton-wool on the evening before examination, in order to produce some local mechanical irritation. Such mechanical irritation is far preferable to chemical irritation with Lugols solution. I have also tried to produce hyperæmia with the combined injection of anterior and follicular hormones with the intent of bringing to light any gonococci that might still be present. This method has no advantage.

In respect of the specificity of the vaccine treatment, it should be stressed that often a single injection leads to a permanent cure of the disease. Of no other form of treatment hitherto used can this be said, be it fever therapy with malarial infection, killed vaccines or a single application of a local remedy. The engendering of febrile conditions during treatment with live vaccines is considered undesirable and possible rises in temperature should be anticipated by prophylactic doses of salicylates. The only factors which could be so markedly effective in such a single treatment are the proteins and toxins liberated by the breaking down of the gonococci injected into the skin. These are the specific antibodies.

The gonococcus is implanted into tissue—skin—which normally it is not in the habit of entering, being unable of itself to ensconce there. In the skin it is as a rule killed within a comparatively short time. The following tests have been made by me. Three, six and twelve hours after the intracutaneous injections, serum was removed from the skin by scarifying the tissue, in order to make a culture on ascites agar plates. As the tissue encircling the site of injection is very inflamed this may be done quite easily. Gonococci could no longer be grown from this serum and it would appear therefore that the gonococci had been killed off very quickly in the tissues. After excision of these skin portions, two to three months after treatment, histological examinations were carried out (Professor Robert Mayer, Universitäts-Frauenklinik, Berlin) without gonococci being found. There have been cases in which gonococci have continued to live for fourteen days, causing an abscess to form at the site of injection, but this will be discussed later. The moribund gonococci throw off into the tissues their endo- and

## BRITISH JOURNAL OF VENEREAL DISEASES

ecto-toxins such as are found also in old gonococcal cultures and gonococcal filtrates, thus producing a condition of immunisation. A comparison of the serum of women treated with injections of live vaccine and that of healthy women, when mixed with nutrient agar, showed no difference in their behaviour. We evoke in the human tissues all these antibodies which can be extraneously introduced by the injection of gonococcus toxins, anti-toxins and other products found in the filtrate of a gonococcus culture. But there is one important difference in the case of our active immunisation, namely, that all these antibodies are produced *in statu nascendi* and in much larger and lasting quantities than would be available by injecting similar artificial agents prepared outside the body.

*Hence it follows that the skin plays a powerful part in the development of immunising bodies which are produced in increasing abundance and attain increasing efficacy proportional to the length and intensity of the battle raging between tissue and bacteria.*

*One may truly say that the fresher the implanted organism the more intense and immediate will be the immunisation that results.*

It is therefore a very satisfactory sign when the organism is sufficiently virulent to produce a small abscess, as the gonococci will then remain alive for some time, setting up a permanent process of immunisation which will the more rapidly bring about a cure. This explains why investigators like Schroeder and his collaborators, Heyn<sup>16</sup>, Schwab<sup>47</sup>, Thomsen<sup>52</sup> obtained the best results when abscesses formed. Jadassohn also has reported that these types of gonorrhœal prostatitis heal best, where, in the course of treatment an abscess forms on the prostate. Vohwinkel<sup>54, 55</sup> has described other observations of abscess formation following gonococcal vaccination.

Desirable as it is to evoke strong local reactions at the site of injection in order to assure immunisation, there are nevertheless cases which show scarcely any reaction at that site. Such cases are parallel to those observed in smallpox vaccination, where children are sometimes treated three or four times without a local reaction being produced; there are other cases again in which a reaction is characterised by a markedly strong purulent

## ACTIVE IMMUNISATION

breaking-down of tissue and high fever. The reason for these, as for all reactions in active immunisation, is to be found in the constitution of the patient as well as in the nature of the vaccine. This brings us to the principal question.

### CAN INTRACUTANEOUS VACCINATION OF LIVE GONOCOCCI CAUSE DAMAGE ?

*No general infection nor dangerous complications were observed in the 10,102 cases in which live gonococcus cultures were injected into the skin. Amongst the cases in the above table only six complications were reported, i.e., 0.06 per cent., whereas it is well known that in 100 cases of gonorrhœa treated only locally, 0.27 per cent. show metastatic developments.*

The following complications have been noticed up to the present after live gonococcus treatment.

Felke <sup>11</sup>—in one case myositis of the extensor muscle of the upper arm developed and also a case of *ulcus gonorrhœicum serpiginosum*. The author ascribes these conditions to certain gonococcus strains having "tissue affinities" and recommends that strains originating from abscesses or metastatic gonorrhœa should not be used, but he adds that in spite of such occurrences, treatment with live gonococcus injections should not be abandoned since it, particularly in severe cases of chronic gonorrhœa, is superior to any other therapy. Waldeyer <sup>57</sup> treated in all only 27 cases of chronic gonorrhœa; he observed complications in 2 cases, once a deep abscess at the site of injection, in another case, metastatic articular infection. It is rather curious that in such a small number of cases two complications should have arisen. Since the report of Waldeyer gives no particulars respecting the nature of the original organisms nor of the methods employed in making the cultures, it is difficult to voice an opinion. It should be emphasised, however, that after injection of killed gonococcus vaccines as well as after live vaccines articular swellings are often observed, which soon disappear and are of an allergic nature, similar to those which develop after serum injections.

Finally, Thomsen <sup>52</sup> reported a deep-seated abscess in the thigh after intramuscular injection and amongst the private cases reported to me I was informed by Jacobsohn

## BRITISH JOURNAL OF VENEREAL DISEASES

of a large abscess in the upper arm. This makes in all six complications.

In regard to cases of large local abscess formation, the possibility would have to be excluded that no contamination was present when the gonococcus culture was injected. In the cases of articular swelling, it should be remembered that even if metastatic articular affections do develop, such temporary metastases are produced during every other form of treatment.

It has frequently been noticed that a regional lymphangitis or lymphadenitis develops, which clears up after a few days' treatment. No complications are reported following injections with attenuated gonococcus cultures (Gonovitan).

### COULD COMPLICATIONS OF EVERY KIND BE PREVENTED, THUS RENDERING THE THERAPY QUITE HARMLESS ?

The weak point of the treatment is the uncertainty of the constitution of the original material. In the absence of tests upon animals, we cannot know in advance whether we are in possession of a very virulent or, if I may put it so, more harmless gonococcus. When Felke advises the avoidance of strains with tissue affinities, we do not know which strains are of this nature and might thus be likely to produce complications. If we know that amongst 10,000 cases of gonorrhœa 1 case of gonorrhœal sepsis occurs which had not been treated otherwise than with local remedies, and no other case of gonorrhœal sepsis has been observed amongst all these 10,102 cases, one may say that this method of treatment is as harmless as any other form.

Should one wish, however, to avoid even the theoretical possibility of a complication, I suggest the following precaution which I applied in the last series of my cases. Before administering the first dose of 1.5 c.c. of the suspension, *i.e.*, before giving the first therapeutic dose, 0.3 c.c. is injected intracutaneously and one waits to see if any articular pains follow or deep phlegmonous inflammation of the subcutical tissues is visible. Should such happen, one must consider the strain or strains of gonococci used for the cultures as too virulent and therefore unsuitable. I carry out this preliminary injection

## ACTIVE IMMUNISATION

because I like to use strong strains of metastatic gonorrhœa.

### GEOGRAPHICAL CONDITIONS INFLUENCING GONORRHŒA

The same gonococci act differently upon different races in different lands. It has been shown, for instance, that gonorrhœa in negroes leads to a much higher percentage of gonorrhœal sepsis than in white races and that the negro often develops disorders of the cardiac valves. Bacteriologically, we can distinguish about four different varieties of gonococci and we can deduce the virulence of the strains from the macroscopical growth. Respecting the latter, I would mention that in my experience the tough slimy type of strains are the most virulent and the most certain to achieve therapeutic results. Japanese who become infected with gonorrhœa in Europe show a worse prognosis than Europeans. Europeans again catching the disease outside Europe are more seriously affected than when they become infected in their own country. By way of illustration I should like to describe the following case.

I was treating gonorrhœa in a negress who had been infected by a negro. This infection took its course in the urethra and cervix without complications. But the same strain of gonococcus produced in two white women a severe febrile condition of the adnexa. In one of these patients two intracutaneous injections of a strain from herself yielded a quick cure and similar treatment was about to be applied to the other patient when general gonococcal sepsis set in. Two different articular metastases developed and one metastasis on the meninges which was of a type which I had not previously noticed and which resulted in temporary blindness of the eye. This condition was diagnosed by the attendant ophthalmologist (Professor Krueckmann, Berlin) as an œdema caused by gonococci which congested the cerebral meninges surrounding the optic nerve. This case of gonorrhœa, even when the complications had all subsided, remained very obstinate and a cure was eventually slowly brought about in Vienna by one of the most experienced specialists in the field of gonococcal vaccines—Bacura. It was a mere chance that I had not applied treatment with live vaccine earlier; had I done so, the

## BRITISH JOURNAL OF VENEREAL DISEASES

development of gonorrhœal sepsis would assuredly have been ascribed to my treatment.

The severity of gonorrhœa is, however, not only dependent upon the virulence of the strains, but it differs also according to the season. In my fifteen years of experience, I have found that the virulence of the original strain from which the gonococcus cultures are made is the only varying and uncertain factor in the treatment. It happens that a strain used in a certain series of patients will produce good results, the same strain, injected a week later barely evokes a reaction. The dependence of gonococcus strains upon temperature, longevity and culture media affects the virulence and, consequently, the therapeutical results achieved by intracutaneous injections of live cultures.

If in spite of this uncertainty attached to the condition of the original material, such good results were obtained by almost all investigators, it is worth while to compare these results with those obtained from other forms of treatment.

### COMPARISON OF RESULTS WITH VARIOUS OTHER FORMS OF TREATMENT USED IN CHRONIC GONORRHOEA

Artificial malarial infection is claimed to be an ideal form of treatment for all obstinate types of gonorrhœa. One hundred per cent. cures are reported by various authors. One must, however, bear in mind that this treatment cannot be given in the out-patient's department and that it represents a very severe attack upon the general health of the patient. Apart from the many complications which may occur during the course of it, complications which with live vaccine therapy could not happen, such conditions as serious anæmia, immediate collapse, circulatory disturbances, loss of weight may ensue which can be rectified only very slowly. The time taken for this treatment is twice that needed for live vaccine therapy. I believe that only in totally refractory cases should treatment of this kind be decided upon.

Treatment with killed gonococcus vaccines produces more serious general and cardiac reactions than that with live vaccine, it takes longer and does not give better percentage results ; indeed, according to available statistics, the successes are less than those with live vaccine,

## ACTIVE IMMUNISATION

even Bucara, who is much in favour of treatment with killed vaccines ascribes better results to the former.

Similar arguments apply to the treatment of chronic gonorrhœa in women with fever-producing proteins, milk injections or injections with the patient's own blood. Recently it has been tried, by means of apparatus, to raise the body temperature to 104° F. and more (Warren <sup>56</sup>). The reports are not explicit in stating whether such hyperthermic methods produce adequate and permanent results in chronic gonorrhœa. In my tests with Walinsky, I proved that patients with chronic gonorrhœa become temporarily and not permanently free from gonococci when their temperature is raised to 104° F. or more.

Similarly the production of high local temperatures as exemplified in diathermy and heat rods has produced no appreciable results. Short-wave treatment has been abandoned.

What success can be credited to local treatment? As I said at the beginning, locally applied medicaments are unable to reach deep-seated foci. Intramuscular and intravenous agents have not shown equally good results. Medicaments which partly penetrate the surface when applied locally to the cervical canal, may as in the case of Flavadin cause necrosis of that part and the percentage of cures claimed for it is not higher, particularly in cases of purely chronic gonorrhœa with constantly recurring relapses. It is just these severe cases which are difficult to influence in which the live vaccine is indicated. That local treatment may also be applied in addition to live vaccines to kill off the gonococci existing on the surface of the mucosa is, of course, reasonable.

What causes most investigators to give live vaccine thereby the preference over other forms of treatment is the advantage that it may be carried out in the out-patients' department, that the time taken for the treatment is three to four weeks, a shorter time than that needed for other treatments, and that the percentage of cures is higher than that of other methods with the exception of the risky malarial treatment. It must be mentioned that recently (1937) the treatment of gonorrhœa with oral Sulphanilamide (Prontosil) showed a very good therapeutic effect. A derivative of Prontosil "Uliron" seems to be still better, especially in chronic



## BRITISH JOURNAL OF VENEREAL DISEASES

gonorrhœa. Two-thirds of the cases treated in this way reacted favourably.

Live vaccine has achieved unsurpassed success in acute gonorrhœal arthritis.

### INDICATIONS FOR THE TREATMENT WITH LIVE GONOCOCCUS VACCINE

Primarily, it has been selected as the method of choice by all authors in acute and subacute gonorrhœal arthritis. Also in all chronic and obstinate gonorrhœal infections of the cervix, uteri and adnexa. In acute ascending infection the live vaccine may cut short the ascending process. Affections of the ligaments and tendons as well as of muscles which show themselves as due to gonorrhœal rheumatism always respond well. Some authors, as Hussel<sup>10</sup>, have reported good results in acute processes and in vulvo-vaginitis in girls. Other authors again have used the vaccine successfully in pure acute gonorrhœa for the purpose of avoiding complications and with a definite percentage of cures (Bertoloty). I have not had sufficient experience in this field to recommend treatment for such conditions.

My recommendation is to use the live vaccine in all such cases where a gonorrhœal infection of cervix or adnexa of over three months' standing is making no progress in spite of other treatment or where in cervical gonorrhœa acute ascending infection sets in. It should be always used when there is gonococcal infection of the cervix complicated by pregnancy and in acute gonorrhœal arthritis; tentatively in cervical and adnexal gonorrhœa of more than four weeks' standing. This treatment may always be given in the out-patient department accompanied by prophylactic doses of salicylates. If it is not possible to obtain fresh gonococcus cultures, live attenuated vaccines, as presented in Gonovitan, or any other laboratory culture may be used.

### CRITICAL CONSIDERATIONS AND FINAL NOTES

Often chronic gonorrhœal infection finally cures itself, usually after irreparable damage has been caused. The gradual liberation of antigens produced by latent gonococci embedded in the tissues and a process of auto-

## ACTIVE IMMUNISATION

immunisation developed during the course of years, brings this about. Unfortunately, until this happens much permanent damage is done of which the most serious for the woman is sterility. What then was our therapeutic aim, if my understanding of the problem is correct, in order to further such processes of self-immunisation and not allow serious injuries to ensue?

It was to accelerate the long protracted processes of immunisation caused by latent gonococci embedded in the tissues by implanting a focus of active organisms of similar type. The skin offers a solution to this therapeutic problem.

In view of the 10,000 injections of living gonococcus cultures which have been reported up till now and of my fifteen years of investigations supported by the painstaking researches of so many other investigators I feel justified to-day in asking whether this treatment by active immunisation through the injection of living gonococcus vaccines has established itself as a therapeutic measure against gonorrhœa.

Active immunisation with live vaccine surely now presents a mode of treatment for all deep-seated gonococcal infections, whether these are of an acute or chronic type. These deep-seated foci are present in cervical gonorrhœa of not too early origin (in early cervical gonorrhœa there are no deep-seated foci) as well as in adnexal infections of all kinds in man. Further, in acute arthritis, in gonococcal tendovaginitis, neuritis and myositis.

That a vaccine of this kind which can work only in conjunction with the body's power of resistance and is subject to the ever varying character of living immunising organisms, may not always be successful, will be readily understood by all who have studied the nature of vaccines.

(1) In treatments involving over 10,000 injections of live gonococcus cultures 80-85 per cent. cures were effected.

(2) These injections are free from danger. Complications to the extent of only 0.06 per cent. were observed following upon the injections, whereas it is usual for 0.27 per cent. complications to occur in gonorrhœal infections.

(3) The injection of live gonococcus cultures represents

## BRITISH JOURNAL OF VENEREAL DISEASES

an active immunisation which is indicated in the treatment of every deep-seated gonococcal focus, acute or chronic in character.

(4) The treatment may be carried out in the out-patient department and as the sequelæ are slight and of short duration it is superior to every other form of therapy, especially when it is accompanied with mild local treatment.

### BIBLIOGRAPHY

- (1) ABRAHAM, ERNST G : "On Treatment of Chronic Adnex Gonorrhœa with Gonovitan," *Med. Kli.*, 1932, **2**, S. 1108-1111.
- (2) ANTOINE : *Wien. Kli.*, **36**, ii, pp. 883-885.
- (3) BERTOLOTY, RICARDO, and LEOPOLD HERRAIZ : "Active Immunisation in Gonorrhœa by Means of Living Gonococci," *Urologic Rev.*, 1936, **40**, 88-93.
- (4) BUCURA : "Gonorrhœal Infection of the Female Genital Organs," *Handbook, Veit-Stoeckel*, 1934, **8**.
- (5) BUCURA, C. : "Serodiagnose und Vaccinetherapie," *Zbl. f. Gyn.*, 1929, pp. 1693-1700.
- (6) BUCURA : "Ueber Gonokokkenmischvaccinen," *Wien. Klin. Woch.*, 1933, pp. 141-142.
- (7) BUCURA : "Richtlinien zur Behandlung des weiblichen Trippers," *Wien. Med. Woch.*, 1928, **2**, 987 and 1042.
- (8) EDEL, WALTER : "On Treatment of Gonorrhœa with Live Gonococci Vaccine," *Dermat. Zeit.*, **64**, 167-172.
- (9) FEILCHENFELD : "Treatment of Chronic Gonorrhœa with Gonovitan," *Med. Klinik.*, 1932, p. 781.
- (10) FEILCHENFELD : *Dermatolog. Wochenschrift.*, 1933, **2**, 1471-1480.
- (11) FELKE : "Zwischenfälle bei der Go. lebendvaccination," *Med. Klinik.*, 1932, **1**, 644-645.
- (12) FELKE UND V. OETTINGEN : "Zur Anatomie, Immunbiologie und Therapie der Cervixgonorrhœa," *Dtsch. med. Woch.*, 1932, **2**, 1521-1523, and 1936.
- (13) FRANZ, R. : "Handbuch der Haut und Geschlechtskrankheiten Jadassohn," **21**, Jahrgang, 1934.
- (14) FRIEBOES : "Neueste Vaccinationsversuche zur Heilung langdauernder komplizierter Gonorrhœen," *Med. Kli.*, 1931, **1**, 795-796.
- (15) GERGELY, GYORGY : "On the Treatment of Female Gonorrhœa with Gonovitan," *Zbl. f. Gyn.*, **31**, 595-600.
- (16) HEYN : *Zbl. Gyn.*, 1930, Nr. 11, p. 698.
- (17) HESSE UND OBERMAIER : "Wiener Klinik. Woch.," 1929, p. 613.
- (18) HOFSTAETTER, R. : "Ueber die Behandlung durch die Vaccination regional par la porte d'entrée," *Arch. f. Gyn.*, **145**, 794-816.
- (19) HUSSEL, FRITZ : "Erfahrungen bei der Anwendung der Go. Lebendmischvaccine in der Behandlung hartnäckiger und chronischer Gonorrhœe Muenster i. West." *Diss.*, **31**, 8.
- (20) JARECKI : "8, International Cong. Dermat.," Copenhagen, 1930, *und Kli. Woch.*, 1931, Nr. 14.
- (21) KAHN, A. : "Naechst-und Spätresultate der Behandlung von Kranken mit entzündlichen Processen der Uterusadnexe und des

## ACTIVE IMMUNISATION

Peritoneums gonorrhöischer Ätiologie mit lebenden Gonokokkenkulturen," *Ginek*, Nr. 4, 1934 Slo.-22. Russisch.

(22) LANGER: *Dtsch. Med. Woch. und Kli. Woch.*, 1931, Nr. 14. *Sitzungsbericht Berl. Med. Gesellsch.*, February 26th, 1931.

(23) LEVINE UND PINK: *Ann Dermat et Syphilis*, 1933, s. 855. "Sur la valeur diagnostique des injections intracutanées de cultures vivantes et mortes de gonocoques," *Sovietsky Vestnik Vénérologie Dumet*, 1932.

(24) LEVINTHAL, W.: "On Bacteriology of Gonovitan," *Dtsch. Med. Woch.*, 1929, **2**, 1793-1794.

(25) LINDE, E.: "Die Vaccinebehandlung der Gonorrhoe der Frau," *Soviet. Vestnik. Venerol. i. Derm.*, 1935, S. 471, 475.

(26) LINDE UND TIMOCHINA: "Behandlung der komplizierten Frauengonorrhoe mittels lebender Gonokokkenkulturen," *Soviet. Vestnik. Venerol. i. Derm.*, 1933, Nr. 7, S. 519, 526.

(27) LOESER. "Curing Attempts in Gonorrhoea with Fresh Vaccines and Injections of Live Gonococci in Humans," *Zentralblatt f. Gyn.*, 1922, Nr. 46.

(28) LOESER: "The Cure for Chronic Female Gonorrhoea with Fresh Vaccines and Live Vaccines," *Medizinische Kli.*, 1926, Nr. 35.

(29) LOESER: "Session of the Berlin Urological Society," April 27th, 1926, *Zeitschrift fuer Urologie*, **20**, 1926.

(30) LOESER: "The Cure of Chronic Uterus and Adnex Gonorrhoea with Subcutaneous Injections of Live Gonococci (Live Vaccines)," *Med. Kli.*, 1928, Nr. 25.

(31) LOESER: "On Gonorrhoea Treatment," *Kli. Wochenschrift*, 1929, Nr. 29.

(32) LOESER: "Further Experiences in the Treatment of Chronic Gonorrhoea in Females with Live Vaccines (Gonococci Cultures) under Special Consideration of Lasting Results," *Med. Kli.*, 1929, Nr. 3.

(33) LOESER: "The Cure of Chronic Gonorrhoea in the Female by means of a single Subcutaneous Injection of Live Gonococci," *The American Journal of Obstetrics and Gynecology*, St. Louis, 1927, Nr. 3.

(34) "The Treatment of Chronic Gonorrhoea in Females with Subcutaneous Injections of Live Gonococci," *Revue Francaise de Gynecologie L'Expansion Scientifique Francaise*, Paris, 1930.

(35) LOESER: "The Treatment of Chronic Gonorrhoea in Females with Subcutaneous Injections of Live Gonococci according to Experiences from almost 1,500 Injections," *Zentralblatt f. Gyn.*, 1930, Nr. 3.

(36) LOESER: "The Rational Treatment of Chronic Cervix and Adnex Gonorrhoea with Live Vaccines," *Med. Kli.*, 1931, Nr. 22.

(37) LOESER: "Cure of Chronic Gonorrhoea in Females by means of Injections of Live Gonococci," *Vox. medica*, 1929, Nr. 5, Tome. 8.

(38) MUELLER: "Moderne Gonorrhoe Therapie," *Arch. f. Gyn.*, **140**, (600-615).

(39) NAGELL: "Ist. Gonovitan eine Gonokokkenlebendvaccine," *Muen. Med. Woch.*, 1928, **2**, 1961-1962.

(40) NAGELL: *Muen. Med. Woch.*, 1929, Nr. 5.

(41) NARJOKS: *Monatschrift*, 1924, **66**.

(42) PFALZ: *Dtsch. Med. Woch. und Klin. Woch.*, 1931, Nr. 14; *Sitzung der Berl. Med. Gesellsch.*, February 26th, 1931.

## BRITISH JOURNAL OF VENEREAL DISEASES

- (43) POPESCU, BUZEN M.: "Zur Gonorrhöbehandlung durch lebende Gonokokken," *Rev. rom. Urol.*, 1934, **1**, S. 50, 58, Rumänisch.
- (44) SCHULTZ, WOLFHART: "Gonorrhöbehandlung mit Lebendvaccine," *Zentralb. f. Gyn.*, 1935, Nr. 6.
- (45) SCHROEDER: "Grundsätzliches zur Behandlung der Cervixgonorrhoe," *Dermat. Wochens.*, 1931, **1**, 757, 764.
- (46) SCHROEDER: "Die Anatomie der chronischen Cervixgonorrhoe," *Zbl. f. Gyn.*, 1931, pp. 3429-3438.
- (47) SCHWAB, WILLY: "Ueber die Behandlung der Gonorrhoe des Weibes unter modernen Gesichtspunkten," *Kiel Dissertation*, 1931.
- (48) SMIRNOW, N. N.: "Dobrosserdow und R. Rosit. Behandlung der gonorrhoeischen Erkrankungen mittels lebender Gonokokkenkulturen," *Soviet. Vestn. Venerol. i. Dermat.*, **4**, S. 67-75, Russisch.
- (49) SOMMER, STEPHAN: "Ueber intracutane Lebendvaccinebehandlung der weiblichen Gonorrhoe," *Aus der Prager Universitäts-frauenklinik. Monatsschrift f. Geburtshilfe*, Bd. 97, S. 339, 348, 1934.
- (50) STUEMPKE: "Diagnostische und therapeutische Betrachtungen ueber Gonorrhoe," *Med. Klinik*, Jg. 20, Nr. 2, 37-41, Nr. 3, 73-75.
- (51) TACHEZY, RUDOLF: "On the Treatment of Female Gonorrhoea with Injections of Live Gonococci Cultures," *Rozbl. Chir. a Gyn. C. Gyn.*, **11**, pp. 11-15.
- (52) THOMSEN, FRITZ: "Bedeutet die Gonokokkenlebendvaccine einen Fortschritt in der Behandlung der weiblichen Gonorrhoe," *Kiel. Diss.*, 1929.
- (53) TRÈGER, "Therapeutische Versuche bei Gonorrhoe," *Bratislav. lek. Listy*, **13**, S. 505-511, 1933; *Aus der Dermat. Universitätsklinik. Bratislava*.
- (54) VOHWINKEL: "Beobachtungen bei Gonokokkenimpfabcessen," *Verhandlungen 9 Interna Kongress*, Budapest, 1935, pp. 790-793.
- (55) VOHWINKEL: *Arch. f. Derma*, 1933.
- (56) WARREN: *Amer. J. Obstetr.*, 1932, **24**, 592-598.
- (57) WALDEYER: "Pruefung neuer Behandlungsmethoden der weiblichen chron. Go." *Deutsch. Med. Woch.*, 1933, **2**, 1861-1865.
- (58) WOLFF, FRIEDRICH: "Zur Biologie des Gonococcus und zur specifität des Gonovitans," *Dtsch. Med. Woch.*, 1929, **1**, 747.
- (59) WOLFF, FRIEDRICH: "Zur Bacteriologie und Klinik des Gonovitans und der Gonokokkenlebendvaccine," *Klin. Woch.*, 1929, pp. 1496-1497.
- (60) WOLFF: "Lebendvaccine Behandlung der chronischen Gonorrhoe," *Arch. f. Gyn.*, Bd. 132, Kongressbericht, S. 76-79, und 83, 86.
- (61) WOLFF, FRIEDRICH: "Grundsätzliches zur Vaccinetherapie der weiblichen Gonorrhoe," *Beiträge z. Problemen d. Gynäkologie*, S. 89.
- (62) WOLFF, FRIEDRICH: "Vaccinetherapie der weiblichen Gonorrhoe," *Zentral f. Gyn. Jhr.* 48, Nr. 20, 1058-1064; und *Zentral f. Gyn. Jhr.* 50, Nr. 16, 1069-1078; *Med. Klinik*, Jg. 22, Nr. 42, 1610-1614.
- (63) WOLFF: "Klinische Erfahrung bei der Behandlung chronischer Gonorrhoe der Frau mit Gonokokkenlebendvaccine," *Zbl. f. Gyn.*, 1928, pp. 674-686; und *Dtsch. Med. Woch.*, 1928, **2**, 1632-1634.
- (64) WOLFF UND BLUT: *Muench. med. Wochen.*, 1929, Nr. 5.